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10/590,479	07/20/2007	Luigi Giusto Spagnoli	026073-00007	9687

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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/590,479	SPAGNOLI ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/24/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 3-5, 12, 14, 15, 18-20, 22 and 25 have been amended. Claims 1-26 are pending and under consideration.

Specification

The disclosure is objected to because of the following informalities: the spelling error of "glycosilated" rather than "glycosylated".

Appropriate correction is required.

Claim Objections

Claims 2-4, 7 objected to because of the following informalities: the spelling error of "glycosilated" rather than "glycosylated" in claims 2-4; the spelling error of "fluorosceinine" rather than "fluoroscein" and "rodamine" rather than "rhodamine" in claim 7. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 22-26 are rejected under 35 U.S.C. § 101 because they are not presented in the format of a proper process claim. See MPEP 2173.05(q).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 4, 17, 18 and 21-26, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A) The scope of claims 3 and 4 are unclear. Claim 1 requires antibodies that are capable of binding one antigenic epitope of at least one isoform of human clusterin in a selective and specific way. Claim 3 states that the epitope which is being bound is on the non-glycosylated nuclear isoform and comprises SEQ ID NO:2. Claim 4 state that the epitope which is being bound is on the glycosylated cytoplasmic isoform and comprises SEQ ID NO:2. Thus, antibodies which bind to SEQ ID NO:2 will not fulfill the requirements of claim 1 for a selective and specific binding, because antibodies which bind to SEQ ID NO:2 will be cross reactive. Amendment of claim 4 to indicate the appropriate N residue in SEQ ID NO:2 which is glycosylated (page 10, lines 23-26) would overcome this rejection.

(B) The recitation of "tumours" in claims 18 and 21 lacks antecedent basis in claims 15 and 19, respectively.

(C) The recitation of "diagnostic kit" in claim 21 lacks antecedent basis in claim 19.

(D) Claims 22-26 drawn to the "use of at least one of the oligoclonal antibodies defined in claim 1" are vague an indefinite. The claims are drawn to a method of using antibodies, but fails to set forth any active, positive steps that define the claimed method. See MPEP 2173.05(q).

(E) Claims 17 and 26 are vague and indefinite in the recitation of "liquor" without an indication from where said "liquor" is obtained.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 2, 5-10, 15-26 are broadly drawn to antibodies which selectively and specifically bind an antigenic epitope of at least one isoform of human clusterin, including glycosylated isoforms and non-glycosylated isoforms. The instant specification teaches antigenic epitopes SEQ ID NO:1 and 2, which raise polyclonal antisera which bind to a non-glycosylated nuclear isoform found in normal colonic mucosa. The specification teaches that SEQ ID NO:3 and 4, and a glyscosylated form of SEQ ID NO:2 elicits polyclonal antisera which bind to a glycosylated cytoplasmic form of clusterin found in colon carcinoma. The art teaches that clusterin is translated from a single mRNA, and that proteolysis generates amino acid fragments which are linked by five inter-chain disulfide bonds. The art teaches that the subsequent glycosylation is species and tissue-specific and that there exists a great deal of variability in the post-translational modification of clusterin between tissues of the same species (Lakins et al, Journal of Biological Chemistry, 1998, vol. 273, pp. 27887-27895, reference of the IDS submitted August 24, 2006, see page 27887, second column, lines 16-27 and lines 38-42). When given the broadest reasonable interpretation, antibodies that bind to at least one isoform of clusterin includes antibodies that bind to all variations of clusterin, including clusterin in different tissues and species. The description of antibodies that bind to SEQ ID NO:1 and 2 in normal colonic mucosa and antibodies that bind to glycosylated SEQ ID NO:2 and SEQ ID NO:3 and 4 in malignant colon carcinoma fails to describe the genus of antibodies claimed because the genus includes a multitude of different post-translationaly modified clusterin isoforms which cannot be envisioned by the disclosure of the antigenic epitopes of SEQ ID NO:1-4. Further, in light of the teachings of the art regarding the variability of post-translational modification of clusterin as a function of tissue, it would not be expected that the glycosylation pattern observed in colon carcinoma and normal colon mucosa would be the same as the glycosylation patterns found between other normal tissues and their corresponding cancerous counterparts. One of skill in the art would reasonable conclude that applicant was not in possession of the genus of antibodies that selectively bind at least one isoform, because applicant has not adequately described the genus of isoforms to which the antibodies selectively bind.

Further, the claims 1-26 encompass "derivatives thereof". When given the broadest reasonable interpretation, the term "derivative" encompasses alteration of the primary amino acid sequence. One of skill in the art can reality envision a longer fragment of SEQ ID NO:4 taken

from the sequence of clusterin and thus a derivative which encompasses the addition of contiguous amino acid sequence. One of skill in the art can readily envision the addition of a "C" residue at either end of SEQ ID NO:1-4 for conjugation of the peptides to a carrier protein. However, one of skill in the art cannot envision a derivative of SEQ ID NO:1-4 which encompasses alterations in the primary amino acid sequence and which provides a polyclonal antibody which can specifically bind to an isoform of clusterin without first subjecting said "derivative" to an experimental test. Accordingly, it is deeded that the specification lacks an adequate written description of "derivatives thereof".

Claims 16 and 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling the correlation of the malignancy grade in colon cancer with the accumulation of cytoplasmic glycosylated clusterin does not reasonably provide enablement for methods of predicting the grade of malignancy in cancers other than colonic carcinoma. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims..

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re wands, 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The instant specification teaches antigenic epitopes SEQ ID NO:1 and 2, which raise polyclonal antisera which bind to a non-glycosylated nuclear isoform found in normal colonic mucosa. The specification teaches that SEQ ID NO:3 and 4, and a glyscoslyated form of SEQ ID NO:2 elicits polyclonal antisera which bind to a glycosylated cytoplasmic form of clusterin found in colon carcinoma. The specification teaches that the levels of cytoplasmic clusterin are very high in aggressive and metastatic colon carcinoma (page 14, lines 5-6). The art teaches that clusterin is translated from a single mRNA, and that proteolysis generates amino acid fragments which are linked by five inter-chain disulfide bonds. The art teaches that the subsequent glycosylation is species and tissue-specific and that there exists a great deal of variability in the

post-translational modification of clusterin between tissues of the same species (Lakins et al, Journal of Biological Chemistry, 1998, vol. 273, pp. 27887-27895, see page 27887, second column, lines 16-27 and lines 38-42). Thus it would not be expected that the accumulation of cytoplasmic clusterin as envisioned by the instant antibodies which bind to SEQ ID NO:1-4 would provide a nexus for the diagnosis and determination of malignancy grade. the scope of the claims must be commensurate with the scope of the enablement set forth. Given the limited disclosure in the specification that antibodies which bind to SEQ ID NO:1-4 are useful for diagnosing colonic carcinoma and predicting malignancy grade, one of skill in the art would be subject to undue experimentation in order to carry out the methods of claims 16 and 23 with cancers other than colonic carcinomas.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 5-10, 15, 19, 20-22, 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Lakins et al (Journal of Biological Chemistry, 1998, Vol. 273, pp. 27887-27895, reference of the IDS submitted august 24, 2006).

Claim 1 is drawn to polyclonal antibodies able to selectively and specifically bind the antigenic epitope of at least one isoform of human clusterin, said epitope having a length from 10 to 20 amino acids. Claim 2 embodies the antibodies of claim 1 wherein said isoform is a glycosylated cytoplasmic or a non-glycosylated nuclear isoform. Claim 5 embodies the antibodies of claim 1 which are tagged. Claim 6 specifies that the tag is a fluorochrome, a radioactive isotope, an enzyme, biotin or a CL substance. Claims 20 and 21 are drawn to a kit comprising at least one of the antibodies of claim 1.

Claim 15 is drawn to a method comprising the steps of protein extraction, incubation of the extracted protein with one of the antibodies of claim 1; qualitative and quantitative measurement of the antigen-antibody complexes.

Claim 22 is drawn to use of the antibodies of claim 1 for the qualitative and quantitative determination of the level of at least one isoform of human clusterin in a biological sample. Claim 24 specifies that the determination is carried out by ELISA, RIA, immunohistochemistry and Western blot.

Lakins et al disclose a polyclonal antibody, 301, made from peptides consisting of 10-20 amino acids of human clusterin (page 27888, second column, lines 4-9) and a polyclonal antibody, SPG2, wherein the 301 polyclonal bound de-glycosylated clusterin and the SGP2 had bound the glycosylated protein (page 27889, Table I) which meets the requirements of claim 2. Lakins et al disclose Western Blot and immunohistochemistry of deparaffinized prostate tissue sections, wherein said polyclonal antibodies were tagged with biotin by means of a secondary antibody reaction (page 27889, first column, lines 26-30 and lines 38-40). The disclosure of Lakins et al meets the specific embodiments of claims 20 and 21 because intended use of a product is not given patentable weight.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 7-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lakins et al (Journal of Biological Chemistry, 1998, Vol. 273, pp. 27887-27895 in view of Kerr and Thorpe (Immunochemistry LabFax, 1994, pages 118, 128-129, 158).

Claim 7 specifies that the fluorochrome is selected from the group consisting of fluorescein, ficroeritrine, rhodamine, Texas Red and cumarine. Claim 8 embodies the antibodies of claim 6 wherein the radioactive isotope is 14-C or 3-H. Claim 9 embodies the antibodies of claim 6 wherein the enzyme is selected from the group consisting of horseradish peroxidase and alkaline phosphatase.

Lakins et al teach tagging the anti-clusterin polyclonal antibodies with biotin. Lakins et al do not specifically teach any other reagent for tagging the antibodies.

Kerr and Thorpe teach that antibodies can be radiolabeled with Beta-emitters such as tritium for radioimmunoassay (page 118), fluroesceine is the standard green chromophore used to tag antibodies in fluorescent microscopy (page 158), .and that horseradish peroxidase and alkaline phosphatase are coomonaly used in conjugates to antibodies for visualization of antigen-antibody binding (pages 128-129).

It would have been prima facie obvious at the time that the claimed invention was made to label the polyclonal antibodies 301 and SPG2 with 3-H, fluoresceine or an enzyme such as horseradish peroxidase or alkaline phosphatase. One of skill in the art would have been motivated to do so because all these methods were well known in the art as ways of labeling antibodies for immunodetection of antigen-antibody binding as evidenced by Kerr and Thorpe.

All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karen A Canella/
Primary Examiner, Art Unit 1643